THE CLAIMS

What is claimed is:

1. A method of inhibiting TNF-α production which comprises contacting a cell which produces TNF-α with an effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

2. A method of inhibiting PDE4 activity which comprises contacting PDE4 with an effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

3. The method of claim 1 or 2 wherein the cell is a mammalian cell.

4. The method of claim 3 wherein the cell is a human cell.

5. A method of treating or preventing a disease or a disorder ameliorated by reduction of levels of TNF-α in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

6. A method of treating or preventing cancer which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

7. The method of claim 5 or 6 further comprising administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an alkylating agent, nitrogen mustard, a JNK inhibitor, antibiotic,

antineoplastic agent, ethylenimine, methylmelamine alkyl sulfonate, nitrosourea, triazene, folic acid analog, pyrimidine analog, purine analog, vinca alkaloid, epipodophyllotoxin, steroid, a topoisomerase inhibitor, or an anti-cancer vaccine.

8. The method of claim 5, wherein the disease or disorder is diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, mariginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, periphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechet's disease, retinitis, choroiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, rubeosis, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, or 5q- syndrome.

9. The method of claims 6 wherein the cancer is a solid tumor or a blood borne tumor.

10. The method of claim 6 wherein the cancer is multiple myeloma, acute leukemia, lymphoblastic leukemia, myelogenous leukemia, lymphocytic leukemia, or myelocytic leukemia.

11. The method of claim 9 wherein the solid tumor is a tumor of the breast, colon, rectum, colorectum, kidney, or a glioma.

12. The method of claim 5 or 6 wherein the patient is a mammal.

13. The method of claim 5 or 6 wherein the enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is administered parenterally, transdermally, mucosally, nasally, buccally, sublingually, topically or orally.

14. The method of claim 13 wherein the therapeutically or prophylactically effective amount is from about 1 mg to about 5,000 mg per day.

15. The method of claim 14 wherein the therapeutically or prophylactically effective amount is from about 10 mg to about 2,500 mg per day.

16. The method of claim 15 wherein the therapeutically or prophylactically effective amount is from about 100 mg to about 1,200 mg per day.

17. A method of treating or preventing a disease or disorder ameliorated by the inhibition of PDE4 in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

18. A method of controlling cAMP levels in a cell which comprises contacting a cell with an effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

19. The method of claim 17, wherein the disease or disorder is depression, asthma, inflammation, inflammatory skin disease, psoriasis, atopic dermatitis, contact dermatitis, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, inflammatory bowel disease, Crohn's Disease, Bechet's Disease, colitis, chronic bronchitis, allergic rhinitis, arthritis, joint inflammation, ulcerative colitis, atopic eczema, stroke, bone resorption disease, multiple sclerosis, urticaria, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis, arthritic condition, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease,

cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs host reaction, allograft rejection, infection-related fever, myalgia, malaria, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type 1 diabetes mellitus, anaphylactoid purpura nephritis, chronic glomerulonephritis, leukemia, tarditive dyskinesia, yeast infection, fungal infection, condition requiring gastro protection, or neurogenic inflammatory disease associated with irritation or pain.

20. A method of treating or preventing myelodysplastic syndrome in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

21. A method of treating or preventing myeloproliferative disease in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

22. A method of treating or preventing pain in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

23. A method of treating or preventing macular degeneration in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable salt or solvate thereof.

24. The method of any one of claims 17 to 23 further comprising administering to a patient in need of such treatment, prevention or control a therapeutically or prophylactically effective amount of an antihistamine, anti-inflammatory drug, non-steroid anti-inflammatory drug, steroid, anti-cancer agent, hematopoietic growth factor, cytokine, stem call transplantation, or kinase inhibitor.

25. The method of claim 17 wherein the disease or disorder is respiratory disease, asthma, allergic rhinitis, inflammation or chronic pulmonary inflammatory disease.

26. The method of claim 17 wherein the disease or disorder is chronic obstructive pulmonary disease.

27. The method of any one of claims 17 to 23 wherein the patient is a mammal.

28. The method of any one of claims 17 to 23 wherein the enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is administered parenterally, transdermally, mucosally, nasally, buccally, sublingually, topically, or orally.

29. The method of any one of claims 17 to 23 wherein the therapeutically or prophylactically effective amount is from about 1 mg to about 5,000 mg per day.

30. The method of claim 29 wherein the therapeutically or prophylactically effective amount is from about 10 mg to about 2,500 mg per day.

31. The method of claim 30 wherein the therapeutically or prophylactically effective amount is from about 100 mg to about 1,200 mg per day.

32. The method of claim 29, wherein the enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is administered twice a day.

33. A pharmaceutical composition comprising enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, or a pharmaceutically acceptable metabolite, polymorph, salt, or solvate thereof; and a pharmaceutically acceptable carrier, excipient or diluent.

34. The pharmaceutical composition of claim 33 wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, topical or oral administration to a patient.

35. Enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, substantially free of its (+) isomer, or a pharmaceutically acceptable salt or solvate thereof.

36. The enantiomerically pure salt of claim 35 which is a chiral amino acid salt.

37. The enantiomerically pure salt of claim 36 wherein the chiral amino acid is the L isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, N-acetyl-phenylalanine or N-acetyl-leucine.

38. A method of producing enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide which comprises:

(a) contacting *(R)*-3-amino-3-(3,4-dimethoxyphenyl)propionic acid with phthalic dicarboxaldehyde under conditions sufficient to form *(R)*-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionic acid; and

(b) reducing the *(R)*-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionic acid under conditions sufficient to form (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide.

39. The method of claim 38, wherein a chiral amino acid salt of *(R)*-methyl 3-amino-3-(3,4-dimethoxyphenyl)-propionate is contacted with methylene chloride and tetrahydrofuran under conditions sufficient to form *(R)*-3-amino-3-(3,4-dimethoxyphenyl)propionic acid.

40. The method of claim 39, wherein methyl 3-amino-3-(3,4-dimethoxyphenyl)-propionate is contacted with a chiral amino acid under a condition sufficient to form the chiral amino acid salt of *(R)*-methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate.

41. The method of claim 39 or 40 wherein the chiral amino acid is the L isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, N-acetyl- phenylalanine or N-acetyl-leucine.

42. The method of claim 41 wherein the chiral amino acid salt is N-acetyl-L-phenylalanine.

43. An enantiomerically pure salt of (-)-methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate.

44. The enantiomerically pure salt of claim 43 which is a chiral amino acid salt.

45. The enantiomerically pure salt of claim 44 wherein the chiral amino acid is the L isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, N-acetyl-phenylalanine or N-acetyl-leucine.

46. (-)-Methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate N-acetyl-L-phenylalanine salt.